PATENT COOPERATION TREATY

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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY
(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference HDP 5499 PCT	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/EP2004/002810	International filing date *(day/month/year)* 18.03.2004	Priority date *(day/month/year)* 19.03.2003
International Patent Classification (IPC) or national classification and IPC C07H19/20, A61K31/7076		
Applicant HERRMANN, Dieter et al.		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 6 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 3 sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☐	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☒	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
11.08.2004	05.07.2005
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Gohlke, P Telephone No. +49 89 2399-8549

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/EP2004/002810

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

   Description, Pages

   1-26 as originally filed

   Claims, Numbers

   1-8 received on 31.03.2005 with letter of 31.03.2005

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-8
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-8
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-8
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Reference is made to the following citations:

D1: MONTGOMERY J A ET AL: "SYNTHESIS AND BIOLOGIC ACTIVITY OF 2'-FLUORO-2-HALO DERIVATIVES OF 9-BETA-D-ARABINOFURANOSYLADENINE" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 35, no. 2, 1992, pages 397-401, XP001097267 ISSN: 0022-2623

D2: ZAITSEVA G V ET AL: "Convergent syntheses and cytostatic properties of 2-chloro-2'-deoxy-2'-fluoroadenosine and its N<7>-isomer" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, OXFORD, GB, vol. 5, no. 24, 21 December 1995 (1995-12-21), pages 2999-3002, XP004135146 ISSN: 0960-894X

D5: WO 96/15234

Section V:

1. Novelty:

None of the available prior art documents disclose the phospholipid esters of formula (I) of present claim 1.
The subject-matter of claims 1-8 therefore fulfills the requirements of Article 33(2) PCT.

2. Inventive step:

D1 discloses 2'-fluoro-2-halo derivatives of arabinofuranosyladenine (see in particular compound 4d = clofarabine) and their cytotoxicity and biological activity against HIV.

D2 also discloses the cytostatic properties of 2-chloro-2'-deoxy-2'-fluoroadenosine (see compound 7).

The subject-matter of present claims 1-8 differ from D1-D2 in that the therein disclosed

Clofarabine is conjugated to a phospholipid of the form L-B-D wherein:
L is $[R^1\text{-}X\text{-}CH_2\text{-}]\text{-}CH[R^2\text{-}Y\text{-}]\text{-}CH_2\text{-}$,
B is a divalent phosphonat linkage -O-[P(O)(OH)-O]- and
D is clofarabine.

In view of D1-D2, the problem to be solved by present application can be regarded as the provision of nucleoside derivatives exhibiting cytotoxic activity with improved bioavailability (enhanced selectivity and reduced side-effects).

D5 teaches that lipid-nucleoside conjugates of the form L-B-D wherein D is a biologically active compound and L-B is as defined under point 2.1 above, exhibit a significantly enhanced effectiveness and the thus resulting drug-delivery-transport-system is useful to target pharmacologically active substances to target cells and therefore exhibit improved bioavailability (see abstract and pages 8 through 11). Accordingly, this improved bioavailability is due to the fact that a specific enzyme LCE cleaves the L-B-D molecule to form an active monophosphate compound B-D as demonstrated by *in vitro* experiments. Having regard to the comparative data filed by the applicant with letter received on 31.03.2005, the teaching of D5 cannot be generalized, as several nucleoside conjugated of the type L-B-D don't show the desired improved effect *in vivo* (see Exhibits I and II). However as shown in Exhibit III and Table 1 of present application, clofarabine-5'-monophosphate-DMDOPE of present claim 1 exhibits a significantly higher antitumor activity *in vivo* than the unconjugated clofarabine.

Consequently, the subject-matter of claims 1-8 appears to involve an inventive step and therefore fulfil the requirements of article 33(3) PCT.

Section VIII: Clarity:

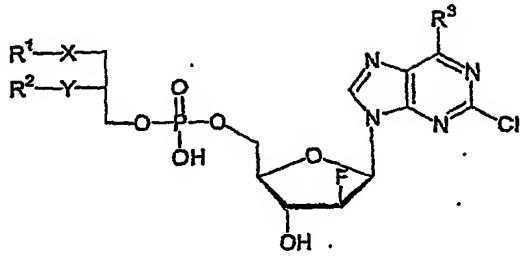
Claims 1-8 relate to phospholipid esters of 9-(2'-deoxy-2'-fluoro-arabinofuranosyl)- 2-chloroadenine.

However, present description refers on page 10 to diphosphate conjugates of formula (V) as part of present invention; this embodiment of the invention does not fall within the scope

of the claims. This inconsistency between the claims and the description leads to doubt concerning the matter for which protection is sought, thereby rendering the claims unclear, Article 6 PCT.

Claims

1. A nucleotide derivative of formula I



(I)

wherein

R^1 is selected from the group consisting of a straight-chain or branched, saturated or unsaturated alkyl chain having 1-20 carbon atoms, which is unsubstituted or substituted at least once by halogen, C_1-C_6 alkoxy, C_1-C_6 alkylmercapto, C_1-C_8 alkoxycarbonyl, C_1-C_6 alkylsulfinyl or C_1-C_6 alkylsulfonyl groups;

R^2 is selected from the group consisting of hydrogen, a straight-chain or branched, saturated or unsaturated alkyl chain having 1-20 carbon atoms, which is unsubstituted or substituted at least once by halogen, C_1-C_6 alkoxy, C_1-C_6 alkylmercapto, C_1-C_6 alkoxycarbonyl or C_1-C_6 alkylsulfonyl groups;

R^3 is amino ~~or OR^4, wherein R^4 is C_1-C_8 alkyl~~;

X is selected from the group consisting of a sulfur atom, a sulfinyl group and a sulfonyl group;

Y is oxygen;

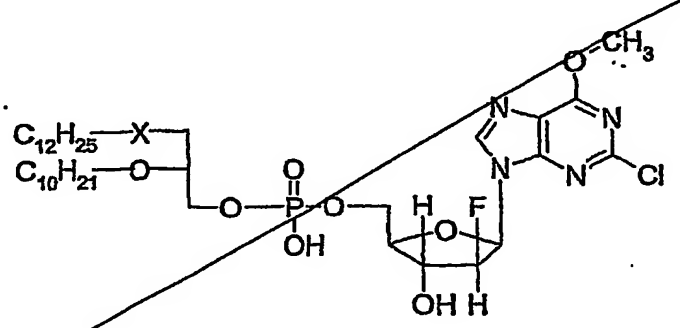
whereby when R^3 is amino, said amino group may be unsubstituted or substituted by a known amino protecting group,
their tautomers, their optically active forms and racemic mixtures, and their physiologically acceptable salts of inorganic and organic acids or bases.

2. The nucleotide derivative according to claim 1, wherein R^1 is a straight-chain C_8-C_{15} alkyl group, which is unsubstituted or substituted by a C_1-C_6 alkoxy or a C_1-C_6 alkylmercapto group.

3. The nucleotide derivative according to claim 1, wherein R^2 represents a straight-chain C_8-C_{15} alkyl group, which is unsubstituted or substituted by a C_1-C_6 alkoxy or a C_1-C_6 alkylmercapto group.

~~4. The nucleotide derivative according to claims 1 to 3, wherein R^3 is OCH_3.~~

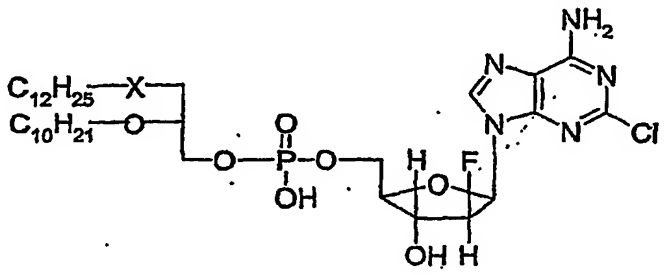
~~5. The nucleotide derivative according the claims 1-4, wherein the compound is:~~



wherein X is sulfur, sulfinyl or sulfonyl.

~~6. The nucleotide derivative according to claims 1 to 3, wherein R^2 is NH_2.~~

4 ~~7~~. The nucleotide derivative according to claims 1 to 3 ~~or 6~~, wherein the compound is:



wherein X is sulfur, sulfinyl or sulfonyl.

5 ~~8~~. A pharmaceutical composition comprising at least one compound according to claims 1 - ~~7~~ 4 in combination with a pharmaceutically acceptable adjuvant or vehicle.

use of a compound according to claims 1–4 for the preparation of a medicam

6 ~~9~~. ~~A method~~ for treating malignant tumors comprising administering to a patient in need of such treatment an amount of a compound according to claims 1 - ~~8~~ 4 effective to treat said tumors.

7 ~~10~~. The ~~method~~ use according to claim ~~8~~ 6, wherein said tumor is selected from the group consisting of carcinomas, sarcomas or leukemias.

The use according to claim 6 – 7

8 ~~11~~. ~~A method for treating malignant tumors comprising administering to a patient in need of such treatment an amount of the composition according to claim 8 effective to treat said tumors~~ in fixed or free combination with other anticancer agents.